# The use of restricted cubic splines to evaluate nonproportional hazards in Cox regression

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# Introduction I

## Cox regression

- Cox regression is the most common regression method for time-to-event data
- An exposure-outcome association is normally quantified into a single hazard ratio (HR)
- A single HR is only meaningful under proportional hazards (PHs)

# Introduction II

## Common approaches to evaluate non-PHs (in Stata)

- Graphically
  - `sts graph`
  - `stphplot`
  - `stcoxkm`

- Numerically
  - `estat phtest`
  - `, tvc(varname)`

# Introduction III

## Common approaches to handle non-PHs (in Stata)

- Piecewise models
  - `stsplit`
  - `, tvc(varname)`
- Stratified models
  - `, strata(varname)`

# Introduction III

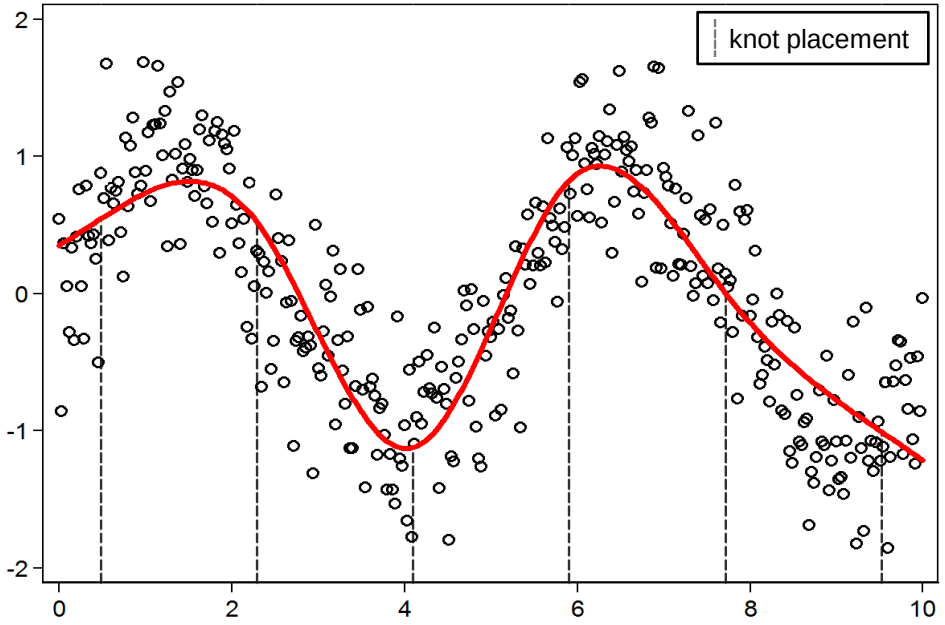
## Common approaches to handle non-PHs (in Stata)

- Piecewise models
  - `stsplit`
  - `, tvc(varname)`
- Stratified models
  - `, strata(varname)`
- Flexible functions
  - Restricted cubic splines (RCS)
  - Fractional polynomials

# Introduction IV

## Cubic splines

- Cubic splines are piecewise-polynomial line segments joined together at knots
- RCS are constrained to be linear before the first knot and/or after the final knot



# Aim of the presentation

- Introduce how RCS can be used in the evaluation of non-PHs in Cox regression
- Present a new Stata postestimation command (`stphcoxrcs`) that greatly facilitates such an evaluation (both numerically and graphically)
- Show a practical example of how to evaluate non-PHs using `stphcoxrcs`

# How to use RCS in the evaluation of non-PHs I

## Preestimation

- First, the analysis time (_*t*) is split into narrow intervals (using `stsplit`)
- Second, a flexible function of _*t* is modeled with RCS (using `mkspline`)
- Third, an interaction is formed between the flexible function of _*t* and the covariate of interest

# Splitting of _t

- Before splitting

| idkod | _d | _t0 | _t |
|---|---|---|---|
| 23011236 | 1 | 74.318256 | 76.538714 |

- After splitting

| idkod | _d | _t0 | _t |
|---|---|---|---|
| 23011236 | 0 | 74.318256 | 74.5 |
| 23011236 | 0 | 74.5 | 75 |
| 23011236 | 0 | 75 | 75.5 |
| 23011236 | 0 | 75.5 | 76 |
| 23011236 | 0 | 76 | 76.5 |
| 23011236 | 1 | 76.5 | 76.538714 |

# How to use RCS in the evaluation of non-PHs I

## Preestimation (cont.)

- First, the analysis time (_*t*) is split into narrow intervals (using `stsplit`)
- Second, a flexible function of _*t* is modeled with RCS (using `mkspline`)
- Third, an interaction is formed between the flexible function of _*t* and the covariate of interest

# How to use RCS in the evaluation of non-PHs II

## Estimation

- A full Cox model is fitted (including the aforementioned interaction terms) (using `stcox`)

$$\lambda(t \mid \mathrm{X}) = \lambda_0(t)\exp(\beta_1 \mathrm{X} + \beta_2 \mathrm{X} \times \mathrm{S}_1(t) + \beta_3 \mathrm{X} \times \mathrm{S}_2(t))$$

# How to use RCS in the evaluation of non-PHs III

## Postestimation

- A joint test of the interaction terms is performed to numerically evaluate non-PHs

$$H_0: \beta_2 = \beta_3 = 0$$

- A graph of the time-varying HRs is created to graphically evaluate non-PHs

$$HR(t) = \exp(\beta_1 + \beta_2 \times S_1(t) + \beta_3 \times S_2(t))$$

# stphcoxrcs

`stphcoxrcs` tests the PH-assumption for a covariate (binary or continuous) using RCS after fitting a model with `stcox`

- *_t* is split using `stsplit` with the options `splitevery(#) | splitat(numlist)`. Default is `splitat(failures)`
- The natural logarithm of *_t* is modeled with RCS using `mkspline` with the option `nknots(#)`. Default is `nknots(3)`

# Practical example I

## Setting and research question

- Data from a prospective cohort of Swedish women (*n* = 32,038; followed-up between 1998-2011)

- Cox regression on the association of fruit and vegetable consumption with risk of symptomatic gallstone disease (*n* = 1120)

- Fruit and vegetable consumption categorized into quartiles of consumption (abbreviated as “fv_cat” in subsequent slides)

# Practical example II

## Cox regression

- `stset`
  - Attained age as time scale

- `stcox`
  - Multivariable-adjusted for potential confounders (omitted from output for clarity)

| _t | Haz. Ratio | Std. Err. | z | P>\|z\| | [95% Conf. | Interval] |
|---|---|---|---|---|---|---|
| fv_cat | | | | | | |
| 2 | 0.96 | 0.08 | -0.47 | 0.6388 | 0.81 | 1.14 |
| 3 | 0.93 | 0.08 | -0.81 | 0.4194 | 0.78 | 1.11 |
| 4 | 0.97 | 0.09 | -0.33 | 0.7388 | 0.81 | 1.16 |

# Practical example II

## Cox regression (cont.)

- `stset`
  - Attained age as time scale

- `stcox`
  - Multivariable-adjusted for potential confounders (omitted from output for clarity)
  - Postestimation: `estat phtest, detail`

| | rho | chi2 | df | Prob>chi2 |
|---|---|---|---|---|
| 1b.fv_cat | . | . | 1 | . |
| 2.fv_cat | 0.01749 | 0.34 | 1 | 0.5603 |
| 3.fv_cat | 0.01998 | 0.44 | 1 | 0.5074 |
| 4.fv_cat | 0.07726 | 6.65 | 1 | 0.0099 |

# Practical example III

## Evaluation of non-PHs using `stphcoxrcs`—test statistics

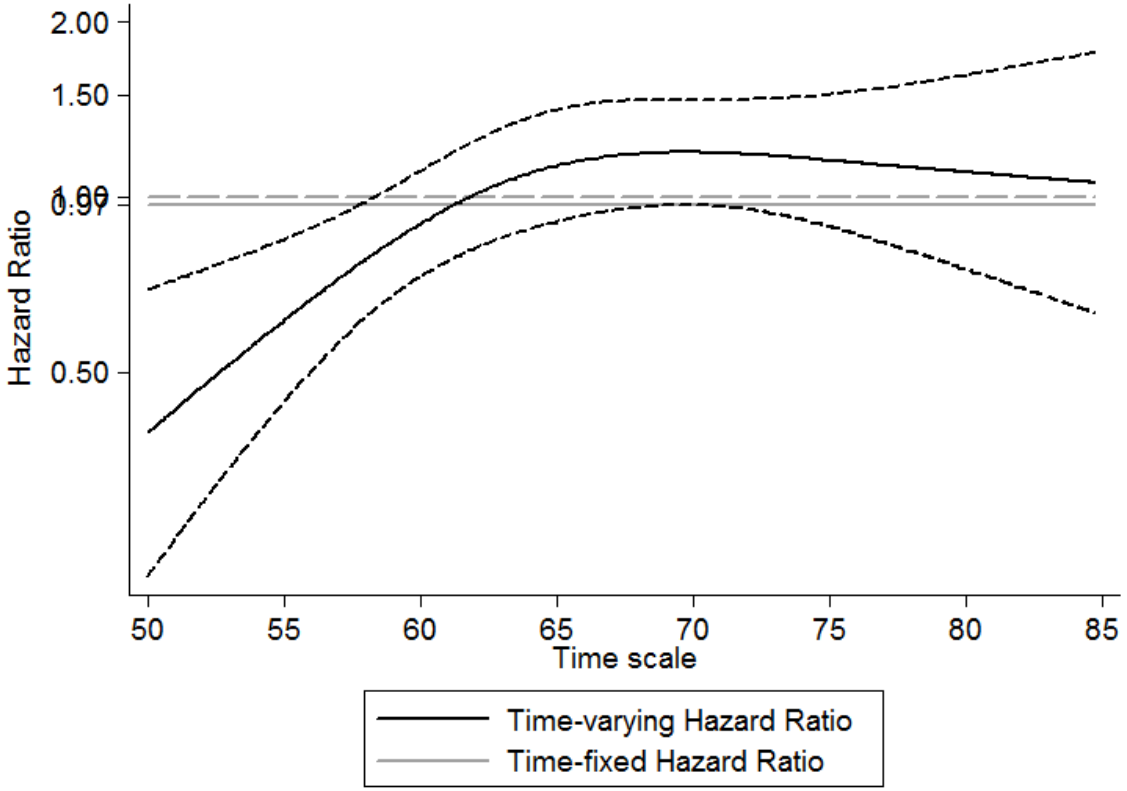
- `stphcoxrcs 4.fv_cat`

```
Wald test of proportional-hazards assumption for i4.fv_cat

    chi2(2) = 12.29
    Prob > chi2 = 0.0021

    Note: time scale modeled using Restricted Cubic Splines with 3 knots
```

# Practical example IV

## Evaluation of non-PHs using `stphcoxrcs`—graphics

- `stphcoxrcs 4.fv_cat`



# Practical example V

## Evaluation of non-PHs using `stphcoxrcs`—options

- Main
  - `nknots(#)`
  - `splitevery(#)`
  - `splitat(numlist)`

- Test statistics
  - `ic`
  - `lrtest`

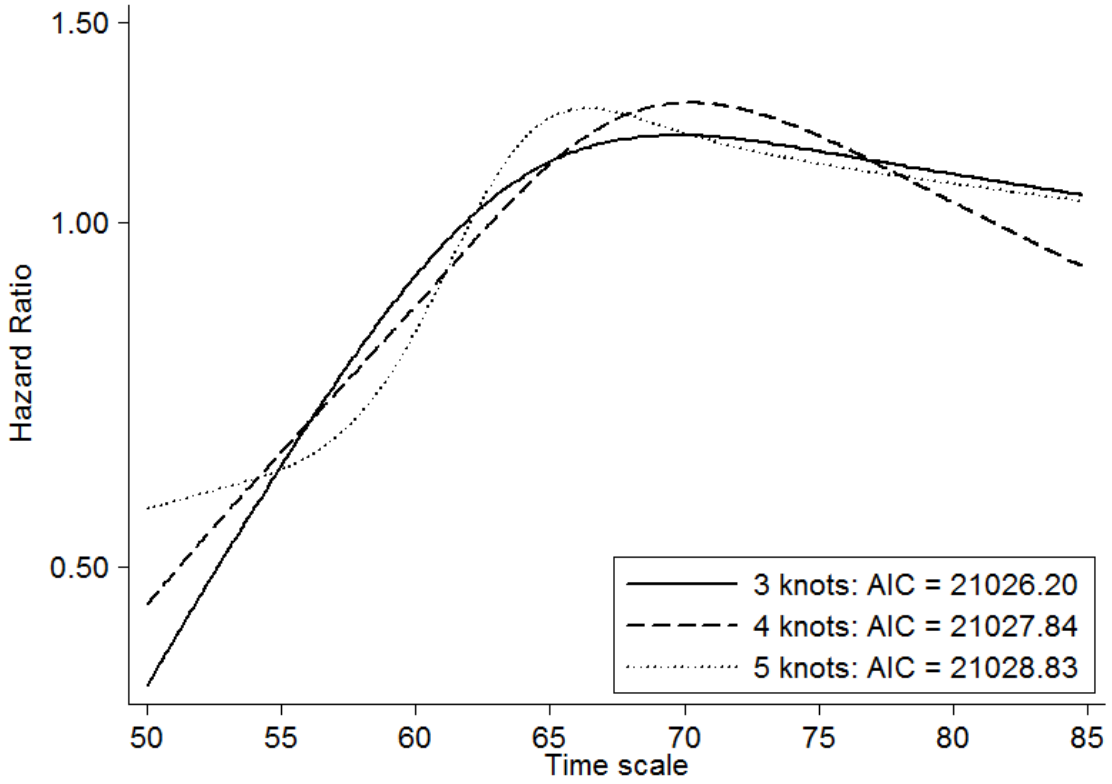
# Practical example V

## Evaluation of non-PHs using `stphcoxrcs`—options (cont.)

- Graphics
  - `level(#)`
  - `range(# #)`
  - `noci`
  - `noyref`
  - `nograph`
  - `gopts(twoway_options)`
  - `saving(filename [, replace])`

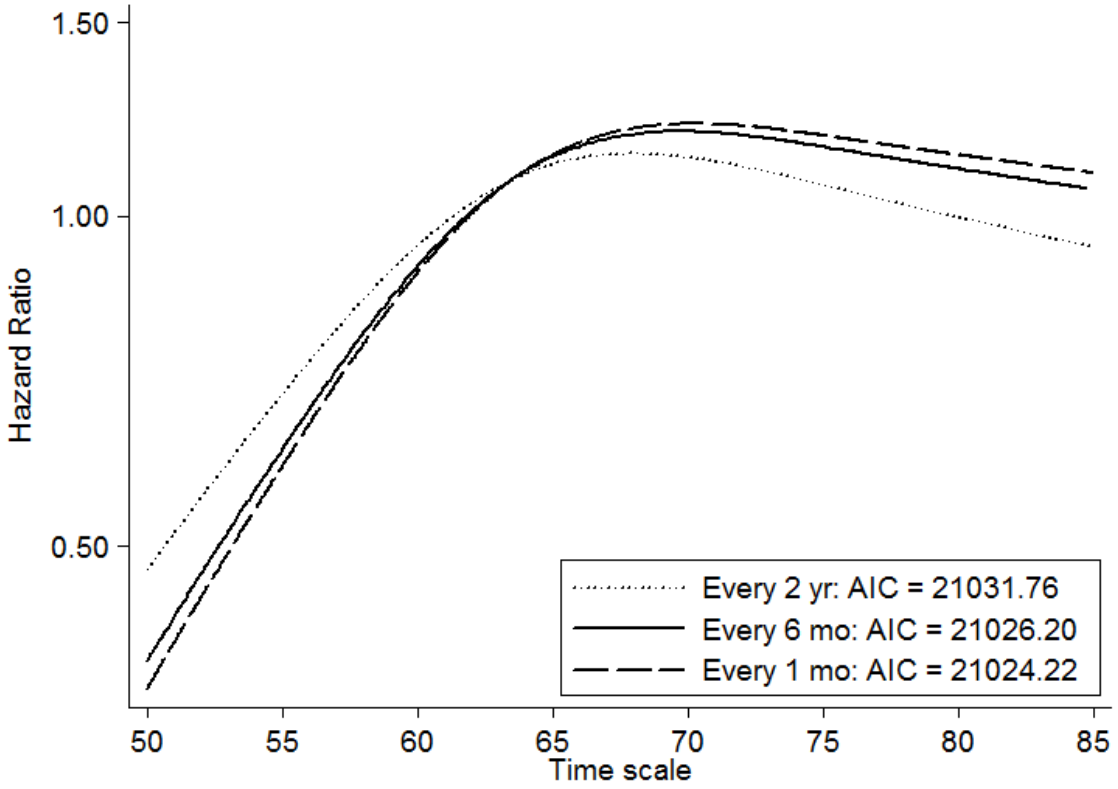
# Practical example VI

Comparison of Cox models with different number of RCS-knots using `stphcoxrcs`



# Practical example VII

Comparison of Cox models with different intervals of *_t* using `stphcoxrcs`



# Summary

- In Cox regression, the assessment of PHs is important for the interpretation of HRs and exposure-outcome associations
- `stphcoxrcs` facilitates the use of RCS in the evaluation of non-PHs (both numerically and graphically)
- It is a useful complement to other approaches that are used to evaluate and/or handle non-PHs

# References


- Heinzl, H., & Kaider, A. (1997). Gaining more flexibility in Cox proportional hazards regression models with cubic spline functions. Computer methods and programs in biomedicine, 54(3), 201-208.

- Therneau, T. M., & Grambsch, P. M. (2000). Modeling survival data: extending the Cox model. Springer-Verlag. New York.

- Royston, P., & Lambert, P. C. (2011). Flexible parametric survival analysis using Stata: beyond the Cox model. Stata Press books.

# Practical example II

## Cox regression (cont.)